REMARKS

Applicants wish to thank Examiners Jamroz and Chan for their time and helpful suggestions given during an interview on March 27, 2002.

Claims 1-23 and 29-57 were pending in the present application. After entry of elections made in response to a restriction requirement, claims 1-6, 8-13, 16-21, 23, 31-36, 38-42, and 45-47 were under consideration. By this amendment, claims 1, 10, 11, 31, and 40 have been amended, and new claims 58-70 have been added. Thus, after entry of this response, claims 1-6, 8-13, 16-21, 23, 31-36, 38-42, 45-47, and 58-70 are currently under consideration.

Support for the amendment of claims 1, 11, and 31 is found in the specification on, *inter alia*, page 3, lines 4-10; and Example 2. Support for the amendment of claims 10 and 40 is found in the specification on, *inter alia*, page 13, lines 14-17; and Example 1. Support for the new claim 58 is found in the specification on, *inter alia*, page 2, lines 2-5. Support for the new claims 59, 62, 65, and 68 is found in the specification on, *inter alia*, page 10, line 24; and page 12, line 22. Support for the new claims 60, 63, 66, and 69 is found in the specification on, *inter alia*, page 1, line 28. Support for the new claims 61, 64, 67, and 70 is found in the specification on, *inter alia*, page 22, Example 2.

With respect to all amendments and cancelled claims, Applicants have not dedicated or abandoned any unclaimed subject matter and moreover have not acquiesced to any rejections and/or objections made by the Patent Office. Applicants reserve the right to pursue prosecution of any presently excluded claim embodiments in future continuation and/or divisional applications.

Attached hereto is a marked-up version of the changes made to the specification and claims by the current amendment. The attached page is captioned "**Version with markings to show changes made**".

Drawings

Applicants acknowledge that drawing submitted do not comply with 37 C.F.R. §1.84. Formal drawings will be submitted when the present application is allowed.

Objection for informalities

Applicants acknowledge that the ® symbol for "GenBank" and "SWISS-PROT" was inadvertently omitted in this application on page 19, paragraph 2. The specification has been amended to include the ® symbol after the trademarks "GenBank" and "SWISS-PROT".

Oath or declaration

The Examiner alleges that the oath or declaration is defective because non-initialed and/or non-dated alterations have been made to the oath or declaration. Specifically, the Examiner points to non-initialed crossing-out of the letter "a" from named inventor Jennie Mather's erroneously spelled name and the non-initialed change of country of citizenship for named inventor Jean-Philippe F. Stephan. A newly executed declaration from Jennie Mather is submitted herewith in compliance with 37 C.F.R. §1.67. Jean-Philippe F. Stephan is not an inventor of the subject matter of the currently pending claims in this divisional application. Therefore, a request to delete Jean-Philippe F. Stephan as inventor pursuant to 37 C.F.R. §1.48(b) is submitted herewith.

Claim rejections under 35 U.S.C. §112, second paragraph

Claims 10 and 40 stand rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

More specifically, claims 10 and 40 are alleged to be indefinite due to use of the terms "ASC, ESC, ROG, BUD, RED, NODD, BR516, RL-65, and NEP" in claims 10 and 40. These terms are well-known to one of skill in the art. Nevertheless, Applicants have amended claims 10 and 40 to remove the terms "ROG", "NODD", "BR516", and "NEP" and have further amended the claims to recite the full cell names of those cells referred to as ASC, ESC, BUD, RED, and RL-65 cells. More specifically, claims 1 and 40 now recite the full name of "ASC"

cells as "adult Schwann cells", the full name of "ESC" cells as "embryonic Schwann cells", the full name of "BUD" cells as "pancreatic epithelial cells from rat e12 embryonic pancreatic buds", the full name of "RED" cells as "pancreatic epithelial cells from rat e17 ductal epithelium", and the full name of "RL-65" cells as "rat lung bronchiolar epithelial cells". Support for these amendments can be found on page 13, lines 11-17.

Based on the above amendments, Applicants submit the claims are now meet the requirements of 35 U.S.C. §112, second paragraph, and request the rejection be withdrawn.

Claim rejections under 35 U.S.C. §112, first paragraph

Claims 10 and 40 stand rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. More specifically, the Examiner alleges that the claimed cell lines ASC, ESC, ROG, BUD, RED, NODD, BR516, RL-65, and NEP are not enabled.

Applicants note that amended claims 10 and 40 no longer recite "ROG", "NODD", "BR516", or "NEP" cells, rendering the rejection as to these cell lines moot.

Applicants submit that U.S. Patent No. 5,721,139 and 5,714,385 provides ample teachings regarding the method to obtain ASC and ESC cells, which are incorporated by reference into the present application. See, page 13, lines 12-13; and page 6, lines 27-30. MPEP §608.01(p) allows incorporation of essential material by reference to a U.S. patent to comply with 35 U.S.C. §112. Both U.S. Patent No. 5,721,139 and 5,714,385 teach the method to obtain the ASC and ESC cell line by culturing dorsal root ganglia (DRG) cells of both adult and embryonic rats in serum-free medium supplemented with specific nutrients and the distinct growth characteristics of the ASC and ESC cell line in response to and production of growth and attachment factors. See Example 1 of both U.S. Patent No. 5,721,139 and 5,714,385. These two patents, U.S. Patent No. 5,721,139 and 5,714,385, are incorporated by reference in its entirety into the present application. Applicants thus submit that the specification of the present

application provides sufficient description of the process to obtain ASC and ESC cells by incorporation by reference to meet the requirement under 35 U.S.C. §112, first paragraph.

Applicants submit that the specification provides ample teachings regarding the method to obtain the BUD and RED cells. Example 1 teaches that the RED cell line can be obtained by using pancreas from rat embryos, culturing in growth media supplemented with specific nutrients, and expanding at 75% confluence after 5-7 days (page 20-21). Example 1 also teaches BUD cells can be obtained by using pancreas from rat embryos, separating the dorsal and ventral pancreatic vaginations, and culturing in the conditions as described for the RED cells (p. 21, lines 28-31). Applicants thus submit that Example 1 provides sufficient description of the process to obtain BUD and RED cells to allow one skilled in the art to make and/or use the cells reproducibly without undue experimentation.

Applicants submit that U.S. Patent No. 5,364,785 provides ample teachings regarding the method to obtain the RL-65 cells, which is incorporated by reference into the present application. See, page 13, lines 22-26. U.S. Patent No. 5,364,785 teaches how to establish the RL-65 cells from rat lungs by culturing rat lung cells in serum-free medium supplemented with specific nutrients and characterize the RL-65 cells. See, Examples 1 and 2 of U.S. Patent No. 5,364,785. As stated above, these teachings can be incorporated by reference into the present application to meet the requirement under 35 U.S.C. §112, first paragraph. MPEP §608.01(p). In addition, a skilled artisan can also obtain RL-65 cells by contacting the American Type Culture Collection (ATCC). RL-65 cells were deposited in the ATCC at 10801 University Blvd., Manassas VA 20110-2209 in February 1990 with a ATCC Deposit Designation of CRL-10354. The deposit of these cells occurred prior the filing date of this application and was deposited under the Budapest Treaty. RL-65 cells were irrevocably released to the public without restriction and condition on January 16, 1995. RL-65 cells are maintained by the ATCC for a period of 30 years after the date of deposit, 5 years after the last request for a sample, or for the enforceable life of the patent whichever is longer.

Based on the foregoing amendments, Applicants submit the claims are now meet the requirements of 35 U.S.C. §112, first paragraph, and respectfully request the rejection be withdrawn.

Claim rejections under 35 U.S.C. §103

Claims 1-6, 8-13, 16-21, 23, 31-36, 38-42, and 45-47 stand rejected under 35 U.S.C. §103(a) as being unpatentable over U.S. Patent 5,932,704 (hereinafter referred to as "the '704 patent"), in view of U.S. Patent 5,714,385 (hereinafter referred to as "the '385 patent").

The '385 patent teaches a method for enhancing the survival and/or proliferation of Schwann cells in serum-free culture media. Although the '385 patent teaches "monoclonal antibodies directed towards the antigen can be produced by any method which provides for the production of antibody molecules by continuous cell lines in culture (see column 10, paragraph 2), the referenced antigen in the '385 patent is a polypeptide, such as mitogenic polypeptide, for use in the culturing techniques disclosed in the '385 patent (see column 9, lines 59-60; and column 19, lines 37-41). Importantly, the '385 patent does not teach or suggest immunization of a host mammal with a "plurality of viable and intact cells of said cell type under conditions which preserve the native configuration of surface antigens on said cells, wherein the surfaces of the cells are free of serum" as is recited in claim 1.

The '704 patent also does not teach or suggest culturing cells in serum-free media or otherwise providing a "plurality of viable and intact cells of said cell type under conditions which preserve the native configuration of surface antigens on said cells, wherein the surfaces of the cells are free of serum" for purposes of immunizing a host mammal to generate a population of monoclonal antibodies that bind to cell surface antigens representative of a specific cell type as is required by claim 1. Rather, the '704 patent teaches using transformed cells or immunogenic peptide as immunogens (column 3, lines 23-24 and line 15, respectively). Furthermore, the '704 specification teaches the use of adjuvants and human serum albumin (column 9, line 66 and column 10 line 8, respectively).

In contrast, Applicants use intact and viable cells wherein "the surfaces of the cells are free of serum" as immunogens instead of immunogenic peptides. Furthermore, the present specification does not use adjuvants for administering the immunogen (intact and viable cells) (see Example 2). The specification is replete with teachings that emphasize the importance of maintaining membrane integrity and preserving cell membrane conformation (*e.g.*, p. 14 lines 10-11). The use of adjuvant, especially well-known and often-used adjuvants such as Freud's adjuvant, would destroy the membrane integrity of the cell and would likely destroy cell membrane conformations as well. Dependent claims 61, 64, 67, and 70 recite the limitation of introducing "into the mammal a plurality of viable and intact cells are without adjuvant".

The Examiner alleges that it would have been *prima facie* obvious to one of ordinary skill in the art at the time this invention was filed to substitute the human adult (ASC) or embryonic Schwann cells (ESC) grown in serum-free media on a biological substrate as taught by the '385 patent in the teachings of the '704 patent to have a method for producing a population of monoclonal antibodies reactive against cell surface antigens. Applicants respectfully traverse this rejection.

In order to render a claimed invention obvious there must be, *inter alia*, some teaching or suggestion, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art to supporting the combination of references. MPEP §2143.01. Neither the '704 patent nor the '385 patent provide the necessary motivation to combine the reference teachings. The present claims are directed to methods for immunizing a host mammal using a "plurality of viable and intact cells of said cell type under conditions which preserve the native configuration of surface antigens on said cells, wherein the surfaces of the cells are free of serum" to produce a population of monoclonal antibodies reactive against a cell surface antigen. The '385 patent does not teach use of serum-free cells as antigens for monoclonal antibody production. Furthermore, the '704 patent does not recognize advantage of serum-free cells as antigens thus one of skill in the art would not be motivated to combine these two references.

In addition, Examiner alleges on page 5 of the office action (Paper No. 14) that there is motivation to combine the references because "(1) '385 cells grown in serum-free media have increased viability and proliferation, and (2) '705 cells used for immunization were viable and expressed high level of receptor and that therefore there is a reasonable expectation of success that '385 cells could be used to raise antibodies." Applicants respectfully submit that the above analysis does not express any motivation to combine at all, but rather confuses two separate requirements of *prima facie* obviousness: motivation to combine and reasonable expectation of success. A reasonable expectation of success, even if established, does not provide the separate requirement of a motivation to combine.

In view of the above, one skilled in the art would not be motivated to combine the teaching of the '385 patent with the teaching of the '704 patent. Therefore, Applicants respectfully submit that a *prima facie* case for obviousness has not been established. Applicants respectfully request that the rejection of claims 1-6, 8-13, 16-21, 23, 31-36, 38-42, and 45-47 be withdrawn and that the claims be allowed as amended.

CONCLUSION

Applicant has, by way of the amendments and remarks presented herein, made a sincere effort to overcome rejections and address all issues that were raised in the outstanding Office Action. Accordingly, reconsideration and allowance of the pending claims are respectfully requested.

If it is determined that a telephone conversation would expedite the prosecution of this application, the Examiner is invited to telephone the undersigned at the number given below.

In the unlikely event that the transmittal letter is separated from this document and the Patent Office determines that an extension and/or other relief is required, applicant petitions for any required relief including extensions of time and authorizes the Assistant Commissioner to charge the cost of such petitions and/or other fees due in connection with the filing of this

document to **Deposit Account No. 03-1952** referencing docket no. 415072000110. However, the Assistant Commissioner is not authorized to charge the cost of the issue fee to the Deposit Account.

Respectfully submitted,

Dated: June 17, 2002

By: _____

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VERSION WITH MARKINGS TO SHOW CHANGES MADE

In the Specification:

Please substitute the following for the paragraphs beginning on page 19 line 6 ending on page 19 line 18:

--The surface antigen recognized by a monoclonal antibody of the present invention can be isolated by a number of processes well known to artisans in the field. Representative procedures are immunoprecipitation and immunoaffinity purification of the target antigens from tissue homogenates or cell lysates. Both methods proceed with binding the target antigens to the monoclonal antibodies that are immobilized onto a solid-phase matrix (e.g. protein A and protein G sepharose beads), followed by separating the bound antigens with the unbound proteins, and finally eluting the antigens from the antibody-coupled solid-phase matrix. Subsequent analysis of the eluted antigens may involve electrophoresis for determining the molecular weight, and protein sequencing for delineating the amino acid sequences of the target antigen. Based on the deduced amino acid sequences, the cDNA encoding the antigen can then be obtained by recombinant cloning methods including PCR, library screening, homology searches in existing nucleic acid databases, or any combination thereof. Commonly employed databases include but are not limited to GenBank®, EMBL, DDBJ, PDB, SWISS-PROT®, EST, STS, GSS, and HTGS.--

In the Claims:

Please amend claims 1, 10, 11, 31, and 40 as follows:

1. (Amended) A method for immunizing a host mammal to produce a population of monoclonal antibodies that bind to cell surface antigens representative of a specific cell type that are heterologous to the host mammal, comprising repeatedly introducing into the mammal a plurality of viable and intact cells of said cell type under conditions which preserve the native configuration of surface antigens on said cells, wherein the surfaces of the cells are free of serum.

10. (Amended) The method for immunizing a mammal of claim 1, wherein the cells are selected from the group consisting of adult Schwann cells (ASC), embryonic Schwann cells (ESC), [ROG,] pancreatic epithelial cells from rat e12 embryonic pancreatic buds (BUD), pancreatic epithelial cells from rat e17 ductal epithelium (RED), [NODD, BR516,] and rat lung bronchiolar epithelial cells (RL-65) (ATCC NO. CRL-10354). [, and NEPcells.]

11. (Amended) A method of generating a plurality of monoclonal antibodies binding to surface antigens of a specific cell type, comprising the steps of:

(a) immunizing a host mammal by repeatedly introducing [with] a plurality of viable and intact cells of a specific cell type that are heterologous to the host mammal under conditions which preserve the native configuration of the surface antigens on said cells, wherein the surfaces of the cells are free of serum;

(b) fusing lymphoid cells from the immunized mammal with an immortalized cell line to produce hybridomas that secrete monoclonal antibodies;

(c) culturing the hybridomas under the conditions favorable for the secretion of monoclonal antibodies; and

(d) selecting the hybridomas that secrete monoclonal antibodies binding to surface antigens present on the viable and intact cells of step (a).

31. (Amended) A method for producing a population of monoclonal antibodies that bind to cell surface antigens representative of a specific cell type that are heterologous to a host mammal, comprising immunizing the host mammal by repeatedly introducing [with] a plurality of viable and intact cells of said cell type under conditions which preserve the native configuration of the surface antigens on said cells, wherein the surfaces of the cells are free of serum; fusing lymphoid cells from the immunized mammal with an immortalized cell line to produce hybridomas that secrete monoclonal antibodies; culturing the hybridomas under the conditions favorable for the secretion of monoclonal antibodies; and selecting the hybridomas that secrete monoclonal antibodies binding to surface antigens present on the viable and intact cells, wherein the surfaces of the cells are free of serum.

40. (Amended) The method for producing a population of monoclonal antibodies according to claim 31, wherein the cells are selected from the group consisting of adult Schwann cells (ASC), embryonic Schwann cells (ESC), [ROG,] pancreatic epithelial cells from rat e12 embryonic pancreatic buds (BUD), pancreatic epithelial cells from rat e17 ductal epithelium (RED), [NODD, BR516,] and rat lung bronchiolar epithelial cells (RL-65) (ATCC NO. CRL-10354). [, and NEP cells.]